Fever of Unknown Origin Associated With Chronic Natural Killer Cell Lymphocytosis

To the Editor: Recently, clinical disorders associated with an increase of large granular lymphocytes in peripheral blood have been identified. These disorders are referred to as "large granular lymphocytic proliferative disorders" [1]. Three subsets of these disorders have been recognized. Those representing neoplastic expansion of cytotoxic T lymphocytes are labelled as "T-large granular lymphocytic leukemias."

Natural killer cells constitute the expanded population of lymphocytes in the other two categories. When a cytogenetic abnormality accompanies an aggressive form of a natural killer cell disorder, frequently with a fatal outcome, the disorder is known as "natural killer cell leukemia/lymphoma" [1]. In contrast, a more indolent form of natural killer cell disorder has been described recently and is clinically akin to T-large granular lymphocytic leukemia [2]. The natural history of this chronic natural killer cell lymphocytosis is indolent, with variable clinical manifestations that include neutropenia, anemia, and vasculitic syndromes. Herein, we describe 2 patients who presented with fever of unknown origin and were subsequently diagnosed with chronic natural killer cell lymphocytosis.

Two men (54 and 78 years old) were examined for recurrent fever. Data from family, social, occupational, and past medical histories of both men were not pertinent. Similarly, results of the following were negative, except that patient 2 had positive IgM serologic findings, with negative cultures and subsequent negative results, for cytomegalovirus: complete physical examination; chemistry profile; urinalysis; chest radiography; peripheral blood, urine, and bone-marrow cultures and special stains (bacterial, mycobacterial, viral, and fungal); bacterial serology for *Brucella, Toxoplasma, Coxiella burnetii, Treponema pallidum,* and *Borrelia burgdorferi;* fungal serology for *Histoplasma, Blastomyces, Coccidioides,* and *Cryptococcus;* and viral serology for Epstein-Barr virus, cytomegalovirus, human immunodeficiency virus, hepatitis B virus, and hepatitis C virus. Screening in both patients for autoimmune diseases, including antinuclear antibody and rheumatoid factor testing, was negative.

In the first patient, the leukocyte count was 7.2×10^9/l, with an absolute lymphocytosis of 4.4×10^9/l and an absolute neutrophil count of 2.1×10^9/l. A peripheral blood smear showed an increased number of large granular lymphocytes. Lymphoid flow cytometry of peripheral blood revealed an increase in the proportion of natural killer cells (68%) (Table I). The patient's condition was treated symptomatically with naproxen (375 mg orally, three times daily), with an unmaintained remission of fever and persistent natural killer cell lymphocytosis.

In the second patient, leukocytes were 8.3×10^9/l, with an absolute lymphocytosis of 4.7×10^9/l and an absolute neutrophil count of 2.2×10^9/l. A peripheral blood smear showed an increased number of large granular lymphocytes. Lymphoid flow cytometry of peripheral blood revealed an increased proportion of natural killer cells (74%) (Table I).

TABLE I. Lymphocyte Subset Analysis in Two Patients With Chronic Natural Killer Cell Lymphocytosis

Variable	Patient 1	Patient 2
Leukocytes, 1×10^9/l	7.2	8.3
Absolute neutrophils, 1×10^9/l	2.1	2.2
Absolute lymphocytosis, 1×10^9/l	4.4	4.7
Natural killer cells ($CD3^-$, $CD16^+$, $CD56^+$), percentage of absolute lymphocytosis	52	74
T-helper cells (CD3, CD4), percentage of absolute lymphocytosis	28	21
T-cytotoxic cells (CD3, CD8), percentage of absolute lymphocytosis	16	23

Naproxen (375 mg orally, three times daily) was prescribed, and the fever, night sweats, and chills resolved. After follow-up of 9 months, the patient remained afebrile despite persistent natural killer cell lymphocytosis (leukocytes, 8.6×10^9/l; absolute lymphocyte count, 4.6×10^9/l; natural killer cell proportion, 77%).

The chronic natural killer cell lymphocytosis demonstrated in these 2 patients was isolated and not associated with any detectable cause. In a recent review of more than 1,500 reports on flow cytometry analyses of lymphocytes in peripheral blood, we found 126 cases (8%) with an increased proportion of natural killer cells [3]. The associated diseases included lymphoproliferative disorders, solid tumors, and skin diseases. A distinct group with a chronic (>6 months) increase of natural killer cells in peripheral blood (chronic natural killer cell lymphocytosis) was described recently, and the associated disease manifestations in some, but not all, patients included chronic neutropenia, severe anemia, and vasculitic syndromes [2]. Because the 2 patients described herein meet the diagnostic criteria for chronic natural killer cell lymphocytosis, fever of unknown origin may be considered one of the manifestations of this disease.

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